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Surface plasmon resonance biosensors for detection of Alzheimer's biomarkers; an effective step in early and accurate diagnosis

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ABSTRACT

The rapid and direct detection of biomarkers in biofluids at clinically relevant concentrations faces serious limitations to develop diagnostic criteria for neurodegenerative diseases such as Alzheimer's disease (AD). In this regard, the early detection of biomarkers correlated with AD using novel modalities and instruments is at the center of attention. Recently, some newly invented optical-based biosensors namely Surface Plasmon Resonance (SPR) has been extensively investigated for the detection of biomarkers using a label-free method or by checking interaction between ligand and analyte. These approaches can sense a very small amount of target molecules in the blood and cerebrospinal fluids samples. In this review, the different hypothesis related to AD, and the structural properties of AD biomarkers was introduced. Also, we aim to highlight the specific role of available SPR-based sensing methods for early detection of AD biomarkers such as aggregated β-amyloid and tau proteins. Efforts to better understand the accuracy and efficiency of optical-based biosensors in the field of neurodegenerative disease enable us to accelerate the advent of novel modalities in the clinical setting for therapeutic and diagnostic purposes.

1. Introduction

Alzheimer's Disease (AD) is one of the age-dependent neurodegenerative disorders correlates with the progressive deficiency in cognitive regions particularly visuospatial memory of brain tissue (Loughrey et al., 2019). According to the evidence-based documents, AD is a leading cause of primary memory-associated dementia especially in the elderly population, and is responsible for the reduction of life expectancy by approximately 50% (Larson et al., 2004). To note, AD is characterized by the malfunction of neurons in different brain regions including the cerebral cortex, frontal base, amygdala, hippocampus, and limbic system followed by progressive cortical atrophy (Fig. 1A) (Nelson et al., 2012). Although both Aβ and tau are prerequisites for the pathogenesis of AD disease, the mutation in the tau gene regardless of Aβ alteration could also promote frontotemporal dementia (Small and Duff, 2008). The most frequently used AD-related biomarkers are CSF levels of Aβ42, tau, and P-tau. Low levels of Aβ42 can be detected in CSF with the onset of disease, whereas tau and P-tau levels increase and detectable in long-term courses (Bateman et al., 2012). Among the various known biomarkers available for the diagnosis of AD, the Aβ42/Aβ40 ratio is considered as a reliable index due to the high diagnostic accuracy.

Biosensors are analytical devices for probing the bio-molecules by changing a natural response into electrical or optical signals. Based on the type of transducer, they are commonly classified into electrochemical, optical, piezoelectric sensors, etc (Khalilzadeh et al., 2011; Mansouri et al. 2020a, 2020b). Until now, several sensing techniques have been exploited for early diagnosis of AD including electrochemiluminescence (Liu et al., 2018), fluorometry (Shi et al., 2017), electrochemical biosensors (Negahdary and Heli, 2019), surface-enhanced Raman spectroscopy (Ryzhikova et al., 2019) and surface plasmon resonance (SPR) based biosensors (Špringer et al., 2020). Among them, label-free detection systems like SPR acts in their

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natural forms and are based on the probe of binding-induced refractive index (RI) changes (Carneiro et al., 2020). In SPR analysis, any small mass changes near the gold chip surface can be detected by angle moves of SPR curves in an array format of the modified gold surface (Gelinsky-Wersing et al., 2017).

As a result, this detection system is fairly easy and inexpensive to measure bio-molecules and allows for quantitative study in bio-molecular interactions. SPR optic-based biosensor has been extensively studied for the detection of AD pathologies without the necessity of labeling process and double antibody technique which can easily sense natural forms of molecules in the blood or cerebrospinal fluid (CSF) samples (Springer and Homola, 2012). In neurodegenerative diseases, early diagnosis is integral to optimal implications and slowing disease progression (Ukraintseva et al., 2006). Calling attention, SPR based biosensors are rapid, sensitive, specific, and cost-effective tools for AD biomarkers detection in clinical research.

In this review, the structural properties of AD biomarkers, current AD diagnostic approaches, and bio-sensing techniques including imaging or sensing methods were presented. The main part of this review was dedicated to discussing the potency and practical application of the SPR optical-based sensing method for early diagnosis of AD. In this regard, Tau and Aβ biomarkers and also the aggregation of Aβ detection mechanisms used in SPR were discussed in detail. The most commonly developed SPR biosensors, including immunosensor and aptasensor, are also scrutinized. The review also highlights common localized SPR based biosensor approaches in the sensing of AD biomarkers.

2. Structural properties of Alzheimer's biomarkers

2.1. Amyloid β (Aβ)

Aβ is a misfolded and insoluble peptide with a molecular weight of ~4 kDa and develops cross-β-sheet super-secondary units. It is thought that this structure is resistant to proteolysis (Lu et al., 2013). Molecular investigations revealed that the diameter of toxic Aβ reaches 70–100 A° and the accumulation of non-fibrillar Aβ assemblies actively participates in the promotion of neurodegenerative disorders like AD (Sajjad et al., 2018). As mentioned earlier, there are two common isoforms of Aβ, a soluble Aβ40, and insoluble Aβ42 which increase significantly during AD (Polanco et al., 2018). Aβ peptides form polymorphic fibrils, with molecular structures that strongly depend on growth conditions. Polymorphic fibrils are seen in the *in vitro* milieu in the form of molecular structures like oligomeric and protofibrillar aggregations (Polanco et al., 2018). Recent structural analysis using cryo-electron microscopy revealed that human purified Aβ fibrils are composed of similarly structured protofilaments which are substantially different from *in vitro* Aβ fibril counterpart (Godyń et al., 2016) (Fig. 1B). Also, the pathological conditions and different hypotheses related to AD were discussed in supplementary information.

2.2. Tau protein

Tau protein is one of the main members of microtubules associated proteins (MAP) family which find to a greater extent in axons to promote microtubule polymerization (Mietelska-Porowska et al., 2014). This protein is made of 16 exons and encoded by microtubule-associated protein tau (MAPT) gene located on the long arm of chromosome 17 and participates in microtubules-related dissociation (Fig. S1). Alternative splice of MAPT mRNA in exons 2, 3 and 10 leads to a combination of six tau related isoforms containing 352 to 441 amino acid residues by different expression throughout the brain (Chen et al., 2017). In this regard, acid-based property originates from polypeptide sequences of tau protein which encoded by exons 2 and 3 while positively charged sequence encoded by axon 10, prepare the basic character of tau protein

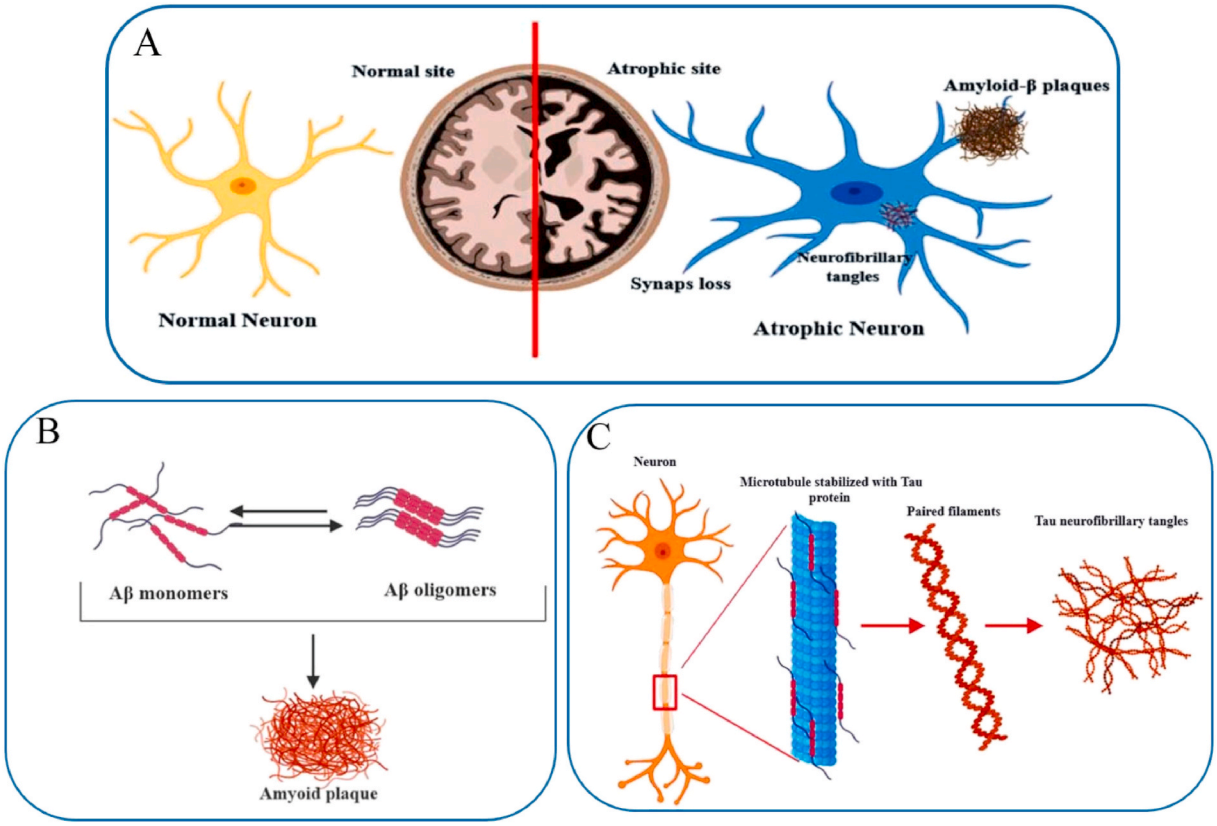

Fig. 1. A. Pathological changes in the brain cortex during Alzheimer's progression. **B.** Amyloid-beta plaque formation following related oligomers accumulation by aging. **C.** schematic tau protein role as microtubule-stabilizer and pathological tau neurofibrillary tangles.

(Nizynski et al., 2017). A difference between six isoforms of tau protein most likely refers to a different number of amino acids in the C-terminal and various insertions of 29 amino acids in the N-terminal of each molecule (Fig. 1C) (Forrest et al., 2017). In clinical settings, 90–95% of frontotemporal dementia (FTD) syndromes by MAPT mutations are related to the FTLD-tau caused by abnormal tau aggregation (Karikari et al., 2019). This abnormality has been reported in patients with less than 50 years old to show disintegration rather than apathy and developed semantic impairment.

3. SPR based biosensors

SPR and localized surface plasmon resonance (LSPR) biosensors have brought a substantial revolution in the detection of biomolecule's experimental settings due to their ability to measure the very insignificant RI change in the surface of gold sensors (Fathi et al. 2018, 2019; Haghaei et al., 2020). In Fig. 2A, the Kretchmann model was exhibited to define the principle of SPR biosensors which included the optical section (light source, prism and gold sensor) and fluidic part (Wilson, 2002). The incident light of laser source is able to excite the free electrons in the gold surface and form the surface plasmon wave between the sensor surface and the fluidic layer (Guo, 2012). SPR or resonance angle defines as an incident angle which related to minimum intensity of the reflected light. The angle of SPR curve moves when a molecules of analyte bind to the immobilized ligand on the gold sensor surface in the evanescent field (a typical depth of near 500 nm) (Fig. 2B). Importantly, in the SPR biosensor platform, the specific biomolecules can be sensed in the form of a response unit (RU) signals by a transducer 10^{-6} refractive index units (RIUs). In SPR curve, 0.1° angle shift corresponds to 1000 RU (Wilson, 2002) (Fig. 2C) . In LSPR-based biosensors, the gold nanostructures can exert a strong ultraviolet–visible (UV) absorption band (Cottat et al., 2013). By measuring the LSPR maximum wavelength shift ($\Delta\lambda max$) before and after adsorption of biomarkers on the silver or gold nanoparticles (GNPs) surface, the selective and sensitive detection of AD biomarkers will be provided (Yang et al., 2013).

3.1. Aβ detection using SPR analysis

In AD, the increased elongation of Aβ42 peptide in the neural cells and subsequent reduction of Aβ2 level to less than 500 pg/ml in CSF is touted as the onset of AD (Humpel, 2011). Therefore, Aβ42 is a very valuable and critical biomarker for determining the prognosis of AD in patients (Hampel et al., 2008). In order to Aβ detection, Lee and colleagues indicated the promotion of signal intensification using GNPs and developed an ultrasensitive SPR-based biosensor for the detection of amyloid (1–40) in CFS with LOD of 1 fg/ml (Lee et al., 2009). The application of diverse nanomaterials such as gold, magnetic, and silver nanoparticles in SPR-based biosensors promotes a significant response in the resonance angle of SPR curves (Tokareva et al., 2004; Wang et al., 2010). For SPR signal enhancement in AD detection, the GNPs–antibody complexes were incubated on each modified gold sensor surface (Lee et al., 2009). The possibility of amyloid fibrils aggregation and an increase of amyloid isoforms (1–40 and 1–42) peptide is thought to be major factors for early detection of AD. In another work, the levels of amyloids (1–40 and 1–42) were monitored in CFS by using immunosensor-based biosensor (Xia et al., 2010). In this study, to enhance SPR signals, a streptavidin-conjugated antibody with the ability to identify N-terminus of the amyloid peptides was used. This approach was able to measure very small amounts of the amyloid peptide, 20 pM, in the CFS samples (Fig. 3A) (Xia et al., 2010). In SPR based systems, modification of SPR chips by Silver (Ag) is an effective approach for intensifying the responses (Liu et al., 2019; Oliveira et al., 2019). Although Ag is quickly oxidized alone but with combination of Au metal, it cannot be oxidized and its reflectance in SPR peak has a thinner line width and sharper slope which led to improve the SPR signals (Lee et al., 2018).

In this line, Lee et al. developed waveguide-coupled bimetallic SPR-based biosensor to detect and measure amyloid β42 in AD (Lee et al., 2014b). With a lot of research, SPR-based chips were upgraded to increase the resolution in the SPR signals by depositing the ZnS–SiO2 waveguide layer between Ag and Au metal layers (Fig. 3B). Using developed immunosensor, amyloid β42 was captured by amyloid β42 antibody on the waveguide SPR chip surface and monitored around the criteria concentration (500 pg/ml) without any labeling (Lee et al., 2014b). Also, a bimetallic SPR chip based gold and silver metals which modified with thiolated protein A was designed for Aβ42 detection (Kim et al., 2019b). Developed bimetallic biosensor was able to detect of low concentrations Aβ42 (39 pg/mL) in comparison of protein A without

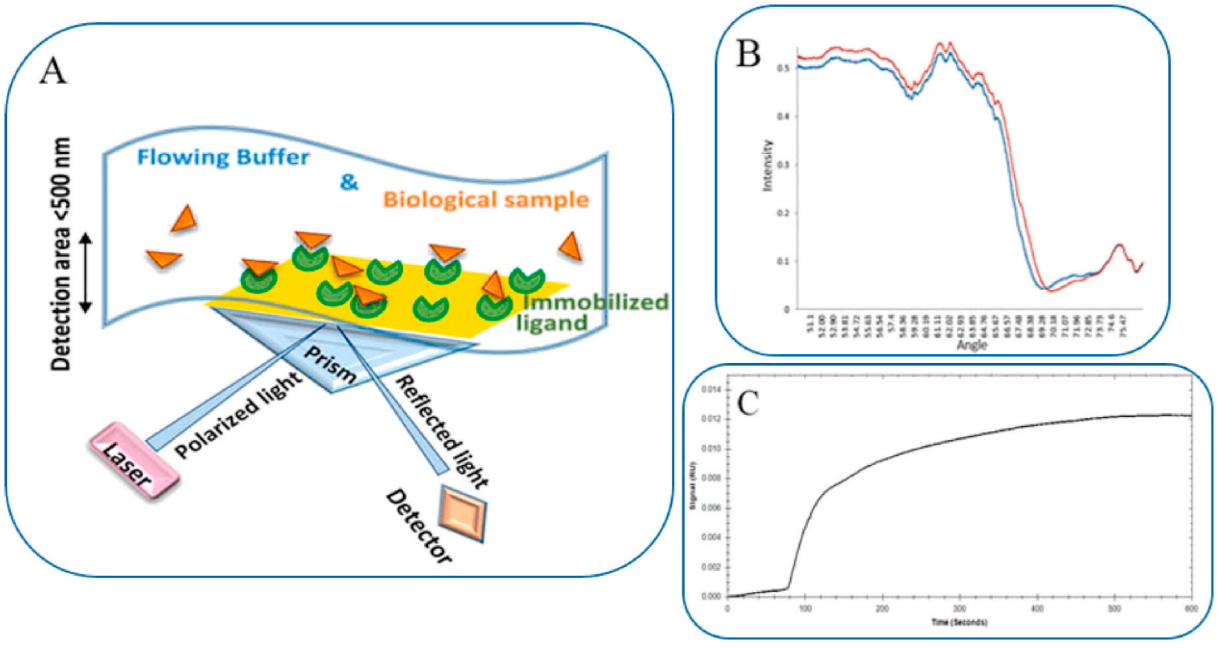

Fig. 2. A. Principles of SPR sensor and schematic illustration in a detection process. **B.** Changes of SPR angle detected by SPR before and after biological molecules binding. **C.** A senogram of a biological molecule adsorption onto a sensor surface in real time (the SPR response unit (RU) versus time).

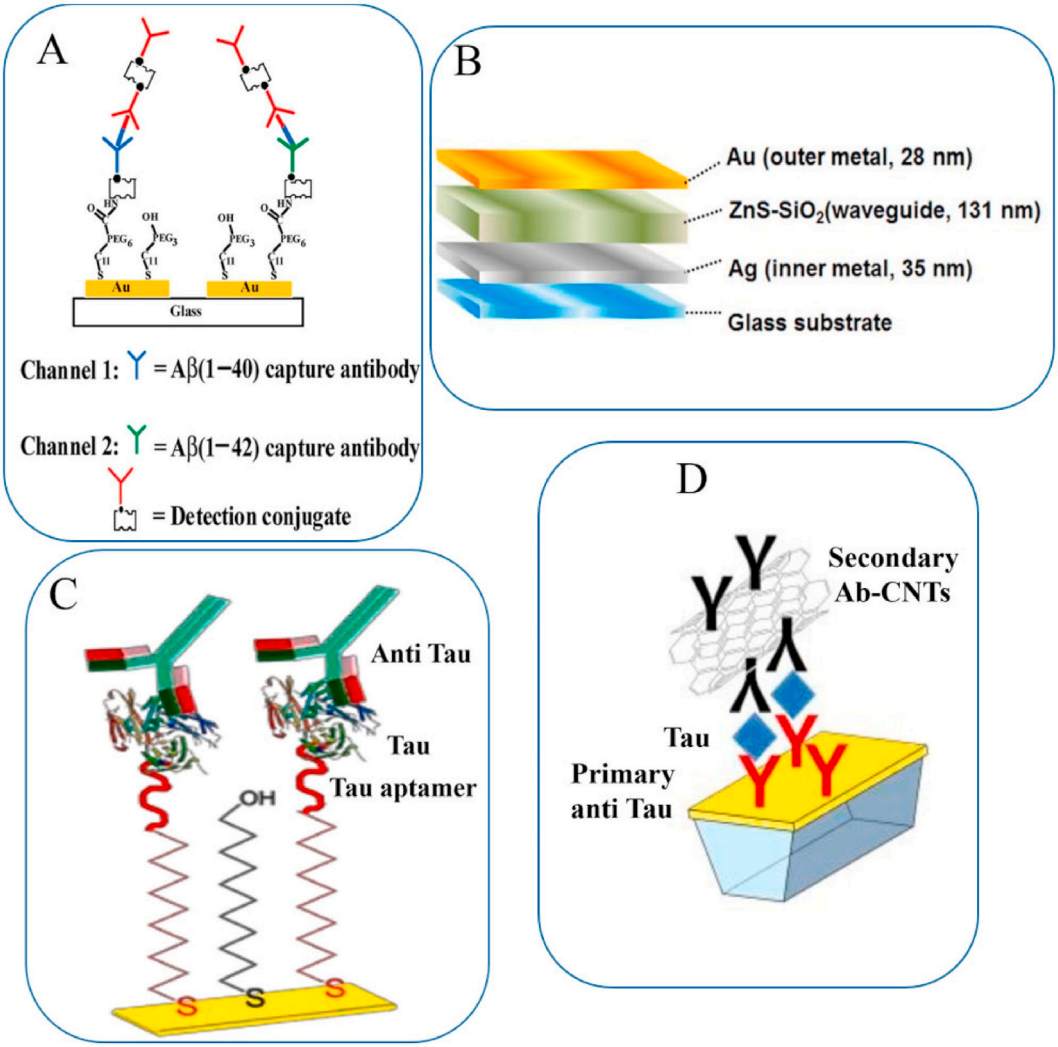

Fig. 3. A. Schematic illustration of showing the simultaneous SPR detection of A (1–40) and A (1–42). Reprinted with permission from (Xia et al., 2010) **B.** Diagram of the SPR sensor system and the wave guide-coupled bimetallic chip configuration. Reprinted with permission from (Lee et al., 2014a) **C.** schematic overview of the strategy for Tau protein detection (MUA, DNA aptamer, and target probes) Reprinted with permission from (Kim et al., 2016b) **D.** Tau coupled to MWCNTs in a sandwich-like format to obtain signal amplification. Reprinted with permission from (Lisi et al., 2017). (MWCNTs: Multi-walled carbon nanotubes).

thiolatiobimetallic.

In Table 1, some studies related to optical-based biosensors for detection of AD biomarkers were summarized.

3.2. Tau detection using SPR assay

Despite the amount of Tau protein increases in the plasma of AD patients (Zetterberg et al., 2013), the limitations of the conventional methods have led to the development of alternative sensitive approaches (Hampel et al., 2010). In 2016, Kim et al. reported a new DNA aptamer/antibody pairing specific to Tau protein for the femtomolar monitoring of Tau in human plasma using a multi-channel SPR platform (Kim et al., 2016b). They developed aptamer modified SPR sensors by immersing bare gold sensors into a thiolated solution like mercaptoundecanoic acid (MUA) and PEG-SH. Thereafter, Tau aptamer was immobilized on sensors using covalent bond formation. In this study, a robust control biosensor in combination with multi-channel measurement capability was designated for simultaneous measurements in AD fluids such as human plasma (Kim et al., 2016b) (Fig. 3C). It seems that metal nanoparticles, carbon-based nanomaterials, such as graphene oxide and carbon nanotubes (CNTs) can promote the SPR signals due to their unique features, such as large molecular weight, extensive surface area, high RI and strong compatible adsorption of biomolecules (Gupta et al., 2019). In line with this statement, sensitive, fast, and specific Tau protein detection was reported in AD via multi-walled carbon nanotubes (MWCNTs) (Lisi et al., 2017). To yield appropriate SPR responses, tau protein-related secondary antibody was modified by MWCNTs and a sandwich strategy for the attachment of secondary monoclonal tau antibody on MWCNTs surface. This method was able to modify LOD from nanomolar ranges in direct tau detection to picomolar ranges in sandwich-based bioassay reaching approximately 10^2 folds (Fig. 3D). With the development of various aspects of the SPR technique, a two-photon scattering assay was developed by using anti-Tau antibody-coated GNPs for the precise detection of Tau (Neely et al., 2009). For example, after the fixation of Tau antibody on the GNPs surface, the complex again was incubated with anti-tau antibody and amine group activation by glutaraldehyde to modify GNPs. The addition of tau protein exhibits a new band peak around 670 nm in UV–vis absorption spectral analyses due to GNPs aggregation by absorption of tau protein on the modified surfaces. In this line, the developed optic-based biosensors were able to diagnose Tau at the levels of 1 pg/mL which is about 2 folds lower than cutoff values (195 pg/mL) in CSF (Neely et al., 2009).

Along with these efforts, in 2018, Vu and colleagues presented SPR

Table 1
Some examples of SPR-based biosensors for the detection of AD biomarkers.

Bio-sensing method	Detected biomarker	Immobilized molecules	Performance parameters	Clinical application of developed biosensor	Ref
Immunosensor	Aβ (1–40)	Antibodies to amyloid (1–40)	LOD: 1 fg/ml	Early detection of AD	Lee et al. (2009)
Immunosensor	Aβ (1–40) and Aβ (1–42)	Antibodies to amyloid (1–40) (1–42)	LOD:20 pM Reproducibility: 10%	Simultaneous quantifications of Aβ in CSF samples from AD patients	Xia et al. (2010)
Immunosensor	Aβ42	The antibody of Aβ 42	LOD: 500 pg/ml Linear range:100 pg/ml to 2000 pg/ml	Developing of WCBIM- SPR method for detection of a critical concentration of AD biomarkers	Lee et al. (2014b)
Immunosensor	Aβ42	Thiolated protein A and the anti-Aβ42	LOD: 39.12 pg/mL Linear range: 50 to 1000 pg/mL	Detection of low concentrations AD biomarkers by protein A- bimetallic SPR chip	Kim et al. (2019b)
Aptasensor	Tau	DNA aptamer specific to Tau or anti-tau agents	LOD:10 fM Linear range:2 pM–80 pM	Detection of human Tau in undiluted plasma	Kim et al. (2016b)
Immunosensor	Tau	Antibody for tau protein	LOD:125pM Reproducibility:14%	AD detection in CSF by signal amplification in MWCNTs	Lisi et al. (2017)
Immunosensor	Tau	Antibody for tau protein	LOD:1 pg/ml Cut of value:195 pg/ml	Rapid and sensitive detection of AD by TPRS assay	Neely et al. (2009)
Immunosensor	Total tau and phosphorylated tau proteins	Antibody TAU5 for total tau and the antibody AT8 for phosphorylated tau	LOD; Total tau: 2.4 pg/ml Phosphorylated tau: 1.6 pg/ml	Blood-based assay to develop POCT in human serum	Nu et al. (2018)
Immunosensor Aptasensor	Tau-Aβ complex	Biotinylated monoclonal anti-Tau and anti-Aβ	LOD:1 pM	Detection of the tau-Aβ complex in CSF samples	Špringer et al. (2020)
	AAT	DNA aptamer specific to AAT	LOD: 10 fM Linear range:10 to 100 fM	DNA aptamer/antibody sandwich assay for detection AD in CSF	Kim and Lee (2015)
Enzymesensor	Acetylcholine	Acetylcholinesterase enzyme	LOD: 38 nM	Acetylcholine detection in clinical samples by Ta2O5 nanoflakes fiber-optic SPR biosensor	Kant and Gupta (2018)
Immunosensor	17- HSD10 enzyme	Antibody against 17-HSD10 peptide	LOD: 50 ng/ml	Detection of 17-HSD10 enzyme in ACSF buffer	Hegnerová et al. (2009)
Immunosensor	APOE	Antibody APOE	LOD: 5–10 μg/ml	Rapidly and specifically the detection of human apoE involved in AD and gastric cancer	François et al. (2011)
Immunoassay	Fibrinogen	Fibrinogen antibody	LOD: 20 ng/ml	In human blood quantitative assay based SPR fiber- sensors	Kim et al. (2016a)

AD: Alzheimer's disease; LOD: Limit of Detection; Aβ: Amyloid-β; WCBIM: Wave guide-coupled bimetallic; SPR: Surface plasmon resonance; MWCNTs: Multi-walled carbon nanotubes; TPRS: Two-photon Rayleigh scattering; POCT: Point-of-care-testing; CSF: Cerebrospinal fluid; ACSF: Artificial cerebrospinal fluid; AAT: Alpha-1 antitrypsin; 17- HSD10: 17 beta-hydroxysteroid dehydrogenase type 10; APOE: Apolipoprotein E.

fiber-based biosensor for the early diagnosis of specific proteins in the serum of AD patients (Nu et al., 2018). The fiber optic sensor-based SPR is a novel biochemical refractometer detection device with non-invasive measurements (Wang et al., 2017b). Generally, the biochemical interactions lead to minor environmental RI changes, while optic fiber-based SPR biosensors are extremely sensitive to these small RI changes (Krishnamoorthy et al., 2010). In the development of SPR fiber immunosensor, the core of a multimode optical fiber was coated by gold layer with nanometer thickness. This biosensor was able to detect total tau and phosphorylated tau proteins with LOD of 2.4 pg/mL and 1.6 pg/mL, respectively (Nu et al., 2018).

Also, a novel sandwich assay combining modified GNPs and SPR systems was developed for the detection of tau protein and Aβ complex (Špringer et al., 2020). This method had a LOD of 0.1 pM for tau-Aβ complex detection in 10% CSF samples.

3.3. Detection of other AD biomarkers

Human apolipoprotein E (apoE) with molecular weight ~39 kD is considered as one of the major determinants in lipid transport and the most significant genetic risk factor for AD. This factor plays a critical role in arteriosclerosis and other diseases including AD or gastric cancers (Sakashita et al., 2008). In this regard, Sciacca et al. developed mission-based fiber SPR structures functionalized with antibodies for rapid and specific detection of apoE (Sciacca et al., 2013). Also for the quantification and detection of ApoE, In 2018 Yi et al. developed a biosensor using SPR. In this research, the gold film surface was modified with ApoE biotinylated DNA probes (Yi et al., 2018). For the complementary sequence, the biotin-streptavidin interaction was delayed and make different SPR responses. This biosensor was able to selectively analyses of ApoE genes in genomic DNA sequences with LOD of 10 fM (Yi et al., 2018).

It is also thought that plasma fibrinogen could be a diagnostic AD indicator and evaluated by optical-based biosensors (Cortes-Canteli et al., 2012; Davalos and Akassoglou, 2012). In this regard, a real-time quantitative immunoassay has been applied to measure systemic levels of fibrinogen in the blood samples of AD patients by using multimode SPR fiber optical biosensors with diagnostic limitations of 20 ng/ml (Kim et al., 2016a). For this purpose, the core surface of the clad-free part of the SPR fiber was covered by using distinct nanoparticles such as silver (Ag) and aluminum (Al). Besides, the histidine-tagged peptide was used to facilitate the oriented immobilization of antibody against fibrinogen in favor of fibrinogen absorption among the other proteins existed in the blood samples (Kim et al., 2016a). A NAD-dependent deacetylase namely Sirtuin 1 (SIRT-1) possesses stress-tolerance properties and has a crucial role in the prevention of AD (Bonda et al., 2011). SIRT not only has a neuroprotective role against stress but also protects experimental animals from AD neurodegenerative pathologies. SIRT-1 levels have been evaluated in blood samples of healthy individuals (either young or old individuals) and AD patients using the SPR approach (Kumar et al., 2013). To this end, the human IgG monoclonal antibody against SIRT1 was immobilized on the carboxydextran modified chips using the amine immobilization method. In this immunosensor, related responses for each sample were recorded based on the ligand concentration which reached around 8.1660.87 ng/ml and 4.8260.4 ng/ml in young and elderly healthy individuals, respectively. It seems that the application of SPR technology has further advantages compare to other immunological methods such as ELISA and western

blotting. For example, the advantage of the SPR technique is based on the reusability of gold chips, high sensitivity, and specificity (Kumar et al., 2013). To date, the interaction between Aβ and 17 beta-hydroxysteroid dehydrogenase type 10 (17- HSD10) is assumed as an indispensable factor in the pathogenesis of AD, such as neuronal cell death and mitochondrial dysfunction (He et al., 1998; Lustbader et al., 2004). Therefore, monitoring 17-HSD10 as a mitochondrial enzyme and possible interaction 17-HSD10-Aβ peptides in biofluids especially CSF exhibits a useful target for the diagnosis of AD. Hegnerová and co-workers have described a direct detection system for measuring the levels of 17-HSD10 using the SPR technique (Hegnerová et al., 2009). They used a multi-channel SPR sensor with spectral modulation which was functionalized with an anti-17-HSD10 polyclonal antibody or myeloid beta using a carboxylic monolayer and amino coupling method. The ng/ml range detection of 17-HSD10 enzyme in CFS buffer was provided by this type of SPR biosensor.

Acetylcholine is considered as one of the organic neurotransmitter compounds whose shortening leads to AD progression in the human brain (Francis, 2005). In this regard, some researchers developed the fiber-optic SPR biosensor containing immobilized acetylcholinesterase (AChE) enzyme on the silver-coated core of plastic-cladded silica (PCS) fiber, (Chand and Gupta, 2007). The detection is based on the principle of competitive binding of the inhibitor for the acetlythiocholine substrate to the enzyme AChE. With the advancement of SPR technology in neurodegenerative diseases, an optical biosensor was also developed for the detection of acetylcholine using the fiber-optic SPR sensing approach (Kant and Gupta, 2018). The sensing probe consisted of multilayers of silver metal and tantalum oxide (Ta_2O_5) nano-flakes modified with acetylcholinesterase enzyme onto the core surface of an optical fiber. The developed biosensors provided a considerable sensitivity of 8 nm/μM as well as a notable LOD value of 38 nM with highly selective towards acetylcholine. Possessing the unique geometric design of Ta_2O_5 nano-flakes combined with superb biocompatibility and chemical stability led to fabricate a highly conducive and efficient platform for enzyme attachment on the sensing surface (Kant et al., 2018). It has been elucidated that Aβ and Tau proteins are the most abundant neurochemical biomolecules in the detection of AD. However, the increase of alpha-1 antitrypsin (AAT) has been also related to the progression of neurodegenerative disease (Song et al., 2009). To detect AAT, a quantitative SPR-based biosensor was developed via the specific binding of AAT onto the DNA aptamer modified gold chip surface (Kim and Lee, 2015). In this method, the application of novel DNA aptamer/antibody sandwich assay pairing specific to AAT protein biomarker has been introduced and this approach successfully measured femtomolar concentrations of AAT in serum samples of AD patients.

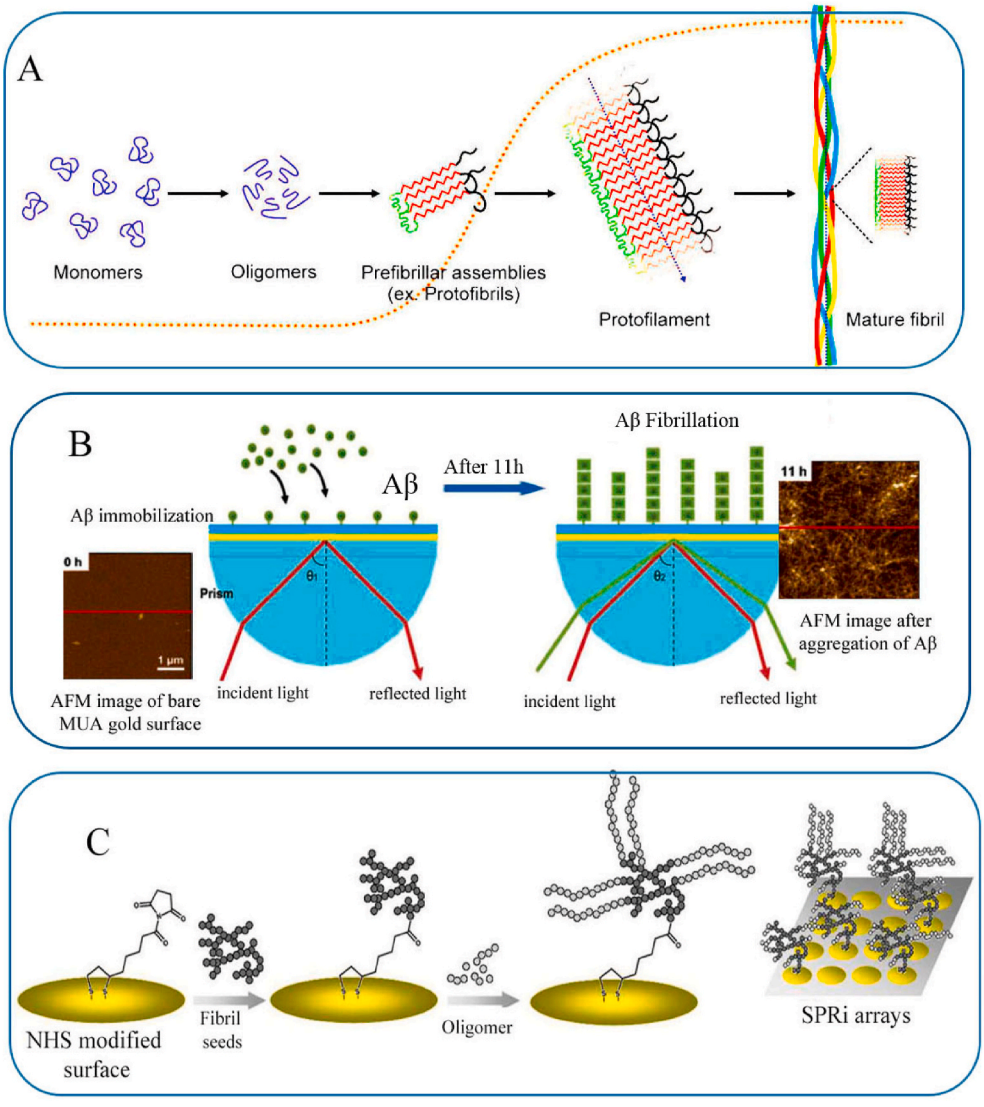

Fig. 4. A. Schematic illustration of amyloid-beta peptide aggregation pathway **B.** Experimental pattern for the SPR analysis of Aβ peptide fibrillation on a gold sensor surface and related AFM images for the aggregation of Aβ. Reprinted with permission from (Ryu et al., 2008) **C.** Experimental flow for monitoring Aβ fibril elongation on 'seed'-immobilized gold spots of an SPRi array. Reprinted with permission from (Cheng et al., 2013) (AFM: atomic force microscopy; MUA: mercaptoundecanoic acid; SPRi: surface plasmon resonance imaging).

3.4. Detection of aggregated Aβ

The aggregation of some proteins like Aβ (1–42), the longest Aβ peptides, is one of the common degenerative pathologies seen in the AD (Hardy and Selkoe, 2002). Aβ aggregation consists of two consequential steps as follows (Fig. 4A); In the lag phase, toxic oligomeric species are formed followed by the second step in which oligomeric peptides elongated/polymerized, leading to the development of fibrils (Arosio et al., 2015). The semi-soluble oligomeric formation of Aβ peptide has an important role in the early stage of aggregated Aβ detection compared to the final insoluble Aβ fibrils plaques (Haass and Selkoe, 2007). Indeed, developing a sensitive and specific method for the discovery of small soluble species applicable in the lag-phase is vital to allow AD early diagnosis and design powerful treatments. Ruy and colleagues studied the AD-related amyloid peptides from fresh monomers to completely grown fibrils by using the *in situ* SPR method (Ryu et al., 2008). They attach Aβ peptide on carboxylated dextran modified SPR sensor surface to evaluate Aβ aggregation after injection of freshly prepared Aβ solution onto the modified gold surface for several hours. Furthermore, the effects of key environmental factors such as the density of attached Aβ peptide, the amount of Aβ peptide in solution phase, and the existence of Fe^{3+} ions were investigated on the promotion of Aβ fibrillation (Ryu et al., 2008). They showed that the existence of Fe^{3+} ions in the Aβ solution enhanced meaningfully denser aggregates and led to a nearly 6-fold increase of SPR responses (Fig. 4B). In Table 2, some factors correlated with Aβ aggregation were outlined. The existence of Tau-Tau interaction and mechanisms related to aggregation in the absence of stimulators was also investigated (Barrantes et al., 2009). Interestingly, SPR and atomic force microscopy (AFM) methods showed Tau-Tau interaction occurred in the absence of any aggregating stimulators. It seems that a much longer time is essential to observe a clear production of filaments as a consequence of the Tau-Tau interaction in the absence of stimulators (Alonso et al., 2001). Along with these investigations, Cheng et al. applied SPR imaging (SPRi) to assess the elongation process of Aβ and exhibited that the fibril formation and elongation are prominently accelerated when Aβ incubated with metals compared to Aβ alone or condition enriched with a well-described polyphenol or epigallocatechin-3 gallate (EGCG) (Cheng et al., 2013) (Fig. 4C).

Fibrillization of the Aβ peptide is closely related to the external inducers such as small elements and different metals (Grelle et al., 2011). For instance, EGCG has been revealed to prevent Aβ aggregation in the brain by chelating metal ions indirectly through accelerating factors to promote disease progression (Bieschke et al., 2010). It has been determined that some metal ions, including Fe^{3+}, Cu^{2+}, $Zn^{2+,}$ and Al^{3+}, possesses more affinity to EGCG (Zhang et al., 2012). According to data from Kraziński et al. study, they reported a simple method for discovering the effect of naturally occurring compounds on the aggregation of Aβ peptide to find potential anti-AD drugs (Kraziński et al., 2011). For this purpose, the SPR gold sensor surface was modified with the Aβ probe using amide bonds formation. Then, alkaloids such as arecoline, trigonelline, pseudopelletierine, pyridoxine, and α-lobeline were injected on the Aβ surface for probing the Aβ aggregation. The proposed biosensor was applied for *in situ* monitoring of the early aggregation procedure of Aβ40 (oligomerization) in the presence of potential aggregation inhibitors. They showed that the highest affinity to the Aβ40 was determined for arecoline and only two alkaloids, α-lobeline, and arecoline, were shown to be potential inhibitors of early Aβ aggregation (Kraziński et al., 2011). Kobayashi and co-workers investigated the pH effect (range from 3.4 to 9.5) in the aggregation and oligomerization of Aβ protein (Kobayashi et al., 2015). They showed that in pH higher than the Aβ isoelectric point (IP), the Aβ aggregation was accelerated by intermolecular ion bridge relay on Asp23 binding with Lys28 amino acids. Additionally, the formation of electrostatic binding between side chains of Asp23 (–COO) and Lys28 ($–NH3^{+}$) is required for aggregation of Aβ at pH between the 6 to 9.5 (Kobayashi et al., 2015). The possible DNA-Aβ interaction was also investigated by SPR based approaches (Barrantes et al., 2007). Data showed that DNA can easily associate with all soluble aggregate forms of Aβ and this ability did not relate to the extent of aggregation. In another work reported by Hu et al. they showed the association and dissociation rate constants for Aβ aggregation in the presence of metal ions (Hu et al., 2006). In this study, soluble Aβ peptide was attached to the gold sensor surface and aggregation induced by the addition of metal ions. The results showed that all the metal ions could promote Aβ aggregation but with different kinetics. For example, Cu^{2+} ions had the greatest association constant with low stability, and Aβ aggregation induced by Fe^{3+} ions had the highest stability compared with Ca^{2+} and Fe^{2+} counterparts (Hu et al., 2006). SPR optic-based biosensors were also used to investigate the aggregation of Aβ peptide on specific antibodies in real-time forms (Palladino et al., 2016). By using the developed SPR method, two different aggregation manners were generated by the soluble oligomers binding to two surface-immobilized antibodies shown which led to the elucidation of the mechanism of self-assembly processes.

Table 2
Some examples of detection of aggregation in AD.

Investigation of …	Aggregation inducers	Obtained result	Ref
Aggregation of Aβ42 peptides	Fe^{3+} ions	Fe3+ ions induced significantly denser aggregates	Ryu et al. (2008)
Aggregation of Aβ40 peptides	Arecoline, Pseudopelletierine,	-Pyridoxine displayed no influence on Aβ40-peptide aggregation	Kraziński et al. (2011)
	Trigonelline -Lobeline And Pyridoxine	-Only two akaloids: A-Lobeline and arecoline displayed potential inhibitors for early Aβ40 aggregation	
Tau-Tau Interaction	No Inducer	Follow the process of aggregation in the absence of aggregating inducers	Barrantes et al. (2009)
Simultaneous Monitor of Multiple Effect of Inducers On Fibril Elongation	EGCG And Various Metals (Fe3+, Cu2+, and Zn2+)	Metals promote the monomer elongation	Cheng et al. (2013)
The pH Effect In The Aggregation And Oligomerization Of Aβ Protein	pH	At 6< pH < 9.5, Aβ monomers begin to aggregate	Kobayashi et al. (2015)
Evaluate The Kinetics Of < Aβ Aggregation/ Dissociation In The Presence Of Metal Ions	Metal Ions:	Metal ions promoted Aβ aggregation but with different kinetics	Hu et al. (2006)
	Cu(II), Ca (II), Fe(II), Fe(III)		

Aβ: Amyloid-β; EGCG: epigallocatechin-3 gallate.

3.5. Localized SPR (LSPR) and AD detection

In recent years, developing biosensors based LSPR had more attention in biomedical sciences (Kim et al., 2018). LSPR is similar to the SPR phenomenon but instead of the gold and metal layer on the glass surface, plasmon resonance is in the GNPs (Jo et al., 2020). Due to the nano-shape structures in LSPR based biosensors, they are more sensitive

than the usual bulk metal thin film-based SPR biosensors. GNPs including gold nano-spheres or nano-rods have been known as a great and excellent characteristic for an LSPR based detection due to its sensitive optical properties on the nanoparticle surface (Unser et al., 2015). LSPR property on the GNPs surface is dependent on the shape, dimensions, and local RI near nanoparticles (Lee et al., 2015). Due to the relation of the λ_{max} position to the size and shape of GNPs, the detection of each biomarker is possible without the need for the labeling process (Truong et al., 2012). Also, in LSPR based biosensor, λ_{max} position shifts by molecular interaction (Ag/Ab binding or DNA hybridization) on the GNPs surfaces by changing in the dielectric environment surrounded on each particle (Hall et al., 2011).

In the work developed by Kim et al. using different sizes and shapes of GNPs like nanospheres and nanorods, an ultra-sensitive platform was designed for the detection of AD biomarkers including two types of Aβ and Tau protein (Kim et al., 2018). In this study for nanoplasmonic biosensor fabrication, GNPs solution was incubated on glass surface coated with aminopropyltriethoxysilane (APTES) for immobilization of AD biomarkers. Also, gold nano-spheres and nano-rods were modified with PEG, EDC/NHS molecules respectively for Aβ and Tau protein monoclonal antibody immobilization on a gold surface. This biosensor determined Aβ 1–40, 1–42, and Tau biomarkers with LOD of 34.9, 26, and 23.6 fM respectively in mimicked blood samples (Kim et al., 2018) (Fig. 5A).

Recently, blood-based detection (Hemo-diagnosis) of AD appears as a hopeful alternative for CFS-based methods due to possessing various kinds of AD biomarkers like Aβ 1–40, 1–42, and Tau protein (Chiu et al., 2014). In this regard, a nanoplasmonic biosensor-based LSPR gold nano-rods were reported with a chaotropic agent for ultrasensitive discovering of AD biomarkers in human plasma of blood samples (Kim et al., 2019a). In developed LSPR assay, guanidine hydrochloride was used as a chaotropic agent and this approach can overcome the difficulties of blood-based AD detection (Fig. 5B). Although the systemic concentrations of Tau protein are 10- to100-fold lower than that of in CSF, this platform can detect tau protein at femtomolar ranges in the blood (Kim et al., 2019a).

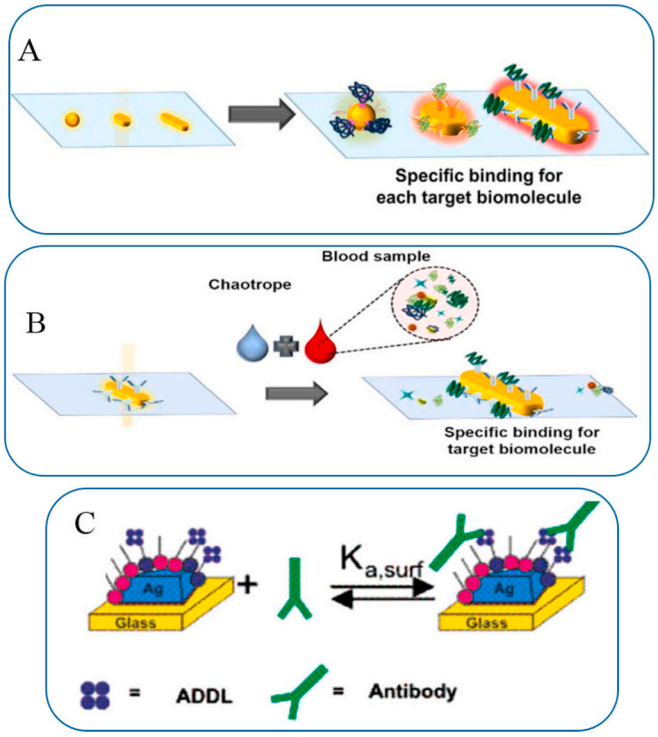

Fig. 5. A. Schematic illustration of LSPR biosensor for multiple AD biomarkers. Reprinted with permission from (Kim et al., 2018) **B.** schematic illustration of nanoplasmonic biosensor system for delicate hemodiagnosis of AD. Reprinted with permission from (Kim et al., 2019a) **C.** Design of the LSPR biosensor for anti-ADDL detection. Reprinted with permission from (Haes et al., 2005) (LSPR: Locolized surface plasmon resonance; ADDL: amyloid β-derived diffusible ligands).

LSPR nano-biosensor using Ag nano-triangles was developed by Haes and colleagues for the detection of amyloid β-derived diffusible ligands (ADDL) which related to AD development (Haes et al., 2004). In general, the nano-sphere lithography (NSL) method was applied to produce Ag nano-triangles in LSPR-based biosensors (Haes et al., 2004). Briefly, polymer microspheres like polystyrene were drop-coated onto the glass templates to form a hexagonal close-packed monolayer on the glass surface. Then, a thin Cr adhesion layer was coated onto the polymer microsphere monolayer. Finally, after Ag sputtering on this surface, the polystyrene nano-sphere was removed by sonication to create individual platforms of the Ag nano-triangles structures on the glass substrate (Gillibert et al., 2018). ADDL-modified Ag nanoparticles have a high selectivity to elevate concentrations of anti-ADDLs (Fig. 5C). The constant for the interaction of ADDLs and anti-ADDLs was 3.0×10^7 M^{-1} (Haes et al., 2004). Others used a nanoscale optical LSPR biosensor to screen the ADDLs in human brain extract and CFS from AD patients to study the oligomerization of small amounts of amyloid proteins (Haes et al., 2005). LSPR-based biosensors were also used for the detection of Tau protein by using gold-capped nanoparticle LSPR immunochip (Vestergaard et al., 2008). The developed LSPR immunochip was also able to detect tau protein with LOD of 10 pg/mL lower than the cut-off value of 195 pg/mL in CSF of AD patients, showing the clinical importance of this factor in the diagnosis of AD samples.

3.6. Current AD diagnosis techniques and advantages of SPR

AD diagnosis is based upon clinical presentation and various criteria such as imaging and fluid biomarkers (Folch et al., 2016). Multiple neuroimaging and molecular assays can be applied to identify abnormalities such as positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT) scan, enzyme-linked immunosorbent assay (ELISA), and Western blotting within the CNS or CSF samples. The advent of novel biosensor-based technologies like electrochemical and optic-based sensing methods contributes to a precise diagnosis. It seems that all these procedures are performed in an invasive manner with high sensitivity and low specificity and considered to be preliminary tools for AD detection in the clinical setting. More details about PET, CT, MRI techniques was presented in supplementary section. The common techniques for detecting Aβ1-42 and tau in CSF samples are ELISA which are less flexible, tedious/laborious assay, and expensive method with an inadequate range of sensitivity for detection of biomolecular markers (Kang et al., 2013). Despite the application of many of these assays to measure AD biomarkers in brain tissue and CSF biological samples, they are relatively expensive, time-consuming, inefficient, and not very sensitive (Balducci et al., 2010). Electrochemical biosensors also have been used for AD detection by transforming chemical signals into a measurable amperometric signal (Shui et al., 2018). For example, Aβ level was detected by electrochemical peptide-based biosensor and ferro/ferricyanide as a redox probe in) in artificial CSF and spiked serum samples (Negahdary and Heli, 2019). Scarlet and co-authors have developed a very sensitive electrochemical biosensor based on Electrochemical impedance spectroscopy (EIS) to detect tau protein (Wang et al., 2017a).

In comparison with available diagnostic neuroimaging, SPR-based diagnosis is postulated as an accurate, non-invasive, and rapid detection of a large number of samples in a single test (Gleerup et al., 2019). For, probing the AD biomarkers in serum fluids, multi-channel test capability for separate and simultaneous control analyses is needed. SPR methods with having multi-channel measurements from 10 channels in the usual SPR device to 100 channels in SPR imaging systems provide real-time and label-free detection for control and test groups separately.

Using SPR optical based methods researchers are able to develop the precise and sensitive analytical approaches for femto-molar range detection of AD biomarkers in patients. In SPR methods using modified surface chemistry, the different ratios immobilization of AD antibodies or nucleic acid aptamers on the SPR gold chips is possible. The commercial availability of SPR sensor chips with different functional groups like carboxylic monolayer in carboxymethyl dextran (CMD) chips, streptavidin, and nitrilotriacetic acid (NTA) sensors allows us the immobilization of protein-ligand with high binding capacity. Using CMD chips the random immobilization of AD-related antibodies by amine groups is provided with minimal non-specific adsorption and denaturation on the chip surface (Mohseni et al., 2016). Also for directed immobilization of AD antibodies, the NTA gold chips can be used via its histidine tag attachment (Knecht et al., 2009). Besides, streptavidin-coated gold chips for biotinylated AD markers results in a more oriented arrangement of protein molecules on the gold surface (Yang et al., 2007).

Also, having the nanostructures on the LSPR sensor surface led to the decrease of signal-to-noise ratio compared with usual microtiter plate analyses. LSPR biosensor in the detection of AD biomarkers provides greatly lower sensitivity to changes in the bulk RI than SPR biosensor, but LSPR biosensors can be strongly matching to SPR based biosensors. The obtained signals of the two methods become like when calculating short-range variations in the RI of molecular adsorption surface on top of the gold chip (Haes and Van Duyne, 2004).

In particular, optical-based biosensors represent a useful and sensitive platform for the probing of the self-assembly Aβ peptide or tau protein when used in combination with immobilized specific target molecules (Pérez et al., 2004). Additionally, the SPR-based methods have been applied to found kinetic models for *in vitro* Aβ fibril development (Cannon et al., 2004). Also, the incorporation of nucleic acid aptamers as an alternative besides modified biochip platforms can measure the multiplexed bioaffinity properties which potentially have the main impact on AD exploration. The advantages and limitations of these methods were shown in Table .3.

4. Conclusions and future perspectives

In AD, some main biomarkers have been defined including Aβ peptide, tau protein in plasma, and to a smaller amount, phosphorylated tau in CSF samples. By emerging the optical chip-based procedures like SPR and LSPR in bio-recognition of molecules, the sensitive and selective detection of AD markers was provided. SPR and LSPR biosensors have brought a substantial revolution in the detection of biomolecule's experimental settings due to their ability to measure the very insignificant mass changes in the surface of gold sensors. Having many advantages in SPR biosensors including label-free detection, real-time monitoring, small sample volume, availability of sensors, rapid response time, reusability, repeatable measurements along with high sensitivity over comes low limitations like mass transport effect, non-specific binding and heterogeneity on the surface sites. Besides, optical-based sensing methods can certify clinical signs with great accuracy, and be a favorable candidate for the high-throughput platform for detecting the multiple biomarkers with the ultra-sensitive and selective format in AD. Also high surface-to-volume ratio of nanostructure arrays in LSPR based biosensors along with available optical diagnostic devices, definitely in the future they will become more compact and efficient bio-sensing tools for AD biomarkers in the POCT systems and health service market. Finally, due to the lack of AD diagnosis tools in specific and early detection, this introduced area has a crucial role and strong potential in the early detection of AD which led to develop of sensitive optical biosensors in further exploration.

Table 3
The advantages and limitations of current AD diagnosis techniques.

Method	Feature	Ref
CT scan	**Usages:** Images from the whole body, Provide beneficial information about the density of the brain in different regions **Limitations:** Exorbitantly expensive, Delivers a high dose of radiation	Takahashi et al. (2019)
MRI	**Usages:** Rapid assay, Effectively detect the structural damages and neural cell death in the brain of the AD patient **Limitations:** Low scanning velocity, Very expensive, Time consuming investigation, Insensitive to the difference between some disease processes	Achterberg et al. (2019)
PET scan	**Usages:** Useful method to track the effectiveness of AD treatment, Classification of disease stage **Limitations:** Hybrid imaging in neurology, Poor spatial resolution, Movements of the patient's head and unreal result	(Chiang, 2018; Huhn et al., 2019)
Fluorescence	**Usages:** Allowed the detection of the four isoforms of tau protein **Limitations:** Having the fluorescent property in molecules, Large sample volume	Lisi et al. (2018)
ELISA	**Usages:** High throughput, Easy to perform by protocols **Limitations:** Temporary readout, Time consuming, Limited antigen information, High amount of protein lysate required	Yang et al. (2013)
Western blot	**Usages:** Separation of AD proteins according to MW, **Limitations:** Work intensive, Low stability, Low throughput, High amount of protein lysate required	Ghosh et al. (2014)
Electrochemical biosensors	**Usages:** High sensitivity, Simple use, Small sample size, Rapid response, and Compatibility Limitations: Narrow or limited temperature range, Limited Lifespan, Do not have the surface architecture	(Monzó et al., 2015; Negahdary and Heli, 2019)
SPR biosensors	**Usages:** Label-free detection, Real-time monitoring, Small sample volume, Availability of sensors, Rapid detection, Reusable sensor chips, Repeatable measurements, Sensitive, Specific, and cost-effective. **Limitations:** Mass transport effect, Heterogeneity of the surface sites, Non-specific binding to surfaces	(Helmerhorst et al., 2012; Schuck and Zhao, 2010)

CT: Computerized tomography; **MRI:** Magnetic resonance imaging; PET: Positron emission tomography; **ELISA:** Enzyme-linked immunosorbent assay; **SPR:** Surface plasmon resonance.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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